



# UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE  
United States Patent and Trademark Office  
Address: COMMISSIONER FOR PATENTS  
P.O. Box 1450  
Alexandria, Virginia 22313-1450  
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|-----------------|-------------|----------------------|---------------------|------------------|
| 10/058,630      | 01/28/2002  | Michael L. Camilleri | 07039-355001        | 3436             |

26191 7590 08/16/2004  
FISH & RICHARDSON P.C.  
3300 DAIN RAUSCHER PLAZA  
60 SOUTH SIXTH STREET  
MINNEAPOLIS, MN 55402

|          |
|----------|
| EXAMINER |
|----------|

STRZELECKA, TERESA E

|          |              |
|----------|--------------|
| ART UNIT | PAPER NUMBER |
|----------|--------------|

1637

DATE MAILED: 08/16/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/058,630

Applicant(s)

CAMILLERI ET AL.

Examiner

Teresa E Strzelecka

Art Unit

1637

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 10 May 2004.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,5 and 8-14 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1,5 and 8-14 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)  
Paper No(s)/Mail Date \_\_\_\_\_.
- 4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date. \_\_\_\_\_.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: \_\_\_\_\_.

### **DETAILED ACTION**

1. This office action is in response to an amendment filed May 10, 2004. Claims 1-5 and 8-14 were previously pending. Applicants cancelled claims 2-4 and amended claims 1, 10, 12 and 14. Claims 1, 5 and 8-14 are pending and will be examined.

2. The rejection of claims 1, 5 and 8-14 under 35 U.S.C. 112, first paragraph, enablement is maintained for reasons given in the "Response to Arguments" section below. The rejection has been restated in view of Applicants' amendments.

### ***Response to Arguments***

3. Applicant's arguments filed May 10, 2004 have been fully considered but they are not persuasive.

Regarding the rejection of claims 1, 5 and 8-14 under 35 U.S.C. 112, first paragraph, enablement, Applicants argue the following:

A) The disclosure is enabling for the amended claims because "...the specification provides significant guidance as to how to determine the presence of the S-HHTTP gene promoter region polymorphism (see pages 5-6 and Example 3, page 13); how to correlate the genotype with diarrhea-predominant IBS patient responsiveness to alosetron using parameters such as colonic transit time (see pages 7-9 and Examples 2, 4, 5, and 6); how to treat patients with diarrhea-IBS having the long/long genotype with alosetron (see pages 9-10); and how to identify patients having diarrhea-IBS for clinical trials for alosetron (see pages 10-11 and the Examples)."

B) With respect to the unpredictability and the Kong et al. reference, Applicants argue that Kong et al. results are based on the correlation of clinical response rather than objective pharmacodynamic endpoint, and the greater responsiveness of the short/short genotype patients is "...in direct contrast with the commonly-accepted mechanism of serotonin uptake in the synapse by

Art Unit: 1637

the transporter protein. As Kong notes on page 3, the deletion allele is associated with decreased gene expression of the transporter protein and decreased serotonin uptake. Decreased uptake by the transporter protein would result in increased serotonin in the synapse, thus rendering any serotonin receptor antagonist less effective (i.e., because of increased competition with serotonin for receptor binding). Thus, the presently claimed methods, and not the Kong methods, are based on the commonly-accepted mechanisms of serotonin uptake and regulation....”

C) Applicants further argue the adequacy of the three references cited in support of the unpredictability factors. Applicants question the Scherl et al. reference as being irrelevant in concluding that the Camilleri et al. study was unable to correlate the serotonin transporter polymorphism with gender-specific alosetron efficacy”. As to the Gershon reference, Applicants argue that it does not matter for the invention whether the mechanisms of the role of serotonin transporter or 5-HT<sub>3</sub> receptor are clear or not. Finally, regarding the Pata et al. reference, Applicants argue that the invention is not about correlating the genotype of the SERT promoter with IBS, but with responsiveness of patients having diarrhea-IBS to alosetron.

Regarding A), Applicants showed the results for 23 patients, which may not be a population sample large enough to account for different percentages of the polymorphisms present in the population and for the variability of symptoms with time for each individual patient, as well as overlap of symptoms with other GI tract disorders. In fact, as pointed by Scherl et al., “Another limitation of the current study was that few of the patients had the short polymorphism, so that this group was underrepresented.” (page 65, last paragraph). As pointed out by Camilleri in a recent review of IBS (Brit. J. Pharmacol., vol. 141, pp. 1237-1248, 2004),

“The practitioner is faced with a syndrome in which symptoms vary greatly between individuals and over time within the same individual.” (page 1238, third paragraph),

“In specialized centers, tests of GI function are available and can provide support for the diagnosis of IBS. However, the results of such tests are certainly not specific, for example, patients with diarrhea from carcinoid tumor present with features suggestive of IBS with diarrhea, and demonstration of rapid transit (von der Ohe et al., 2003) would not identify the presence of a tumor.” (page 1238, last paragraph), and

“ Clinical experience shows two common examples of this principle. The presentation of diarrhea-predominant IBS may be very similar to that of lactose intolerance or celiac disease; in some patients, both conditions may co-exist and contribute to the presentation...” (page 1239, third paragraph).

Therefore, in view of the above references, Applicants’ results on correlation of diarrhea-IBS responsiveness to alosetron with SERT promoter polymorphism are inconclusive, and undue experimentation is required to perform the method as discussed in the rejection.

B) Regarding the Kong et al. reference, the result obtained by Kong et al. was a clinically and statistically valid result, even though it was based on subjects’ assessment of a degree of symptom relief. In fact, this method of measuring the outcome of the clinical trials for patients with functional GI disorders has been officially proposed by the Rome II conference (see van Zanten et al., Gut, vol. 45, pp. II69-II77, 1999, specifically page II72, last two paragraphs and page II73). Further, at least two studies demonstrated that using symptom relief assessment by patients as a measure of outcome in clinical trials provides statistically significant measures of outcome. In particular, Mangel et al. (J. Int. Med. Res., vol. 26, pp. 76-81, 1998) studied responsiveness of 370 patients with IBS to a 5-HT<sub>3</sub> receptor antagonist and evaluated the results based on subjects’ perception of the degree of relief of abdominal pain and discomfort (Abstract; page 77, last two paragraphs; page 78, paragraphs 1-3). The results indicated statistically significant correlation

between responders and non-responders and degree of relief perception (Table 1, for example). In a more recent study, Muller-Lissner et al. (J. Clin. Epidemiol., vol. 56, pp. 310-316, 2003) determined that Subject's Global Assessment (SGA) of Relief, which includes overall well-being, abdominal pain/discomfort and bowel function provides statistically significant results in identifying responders to tegaserod therapy (Abstract; page 311, paragraphs 3-10; page 312, paragraphs 1-6). Again, the effect of 6 mg tegaserod was determined to be statistically significant as compared to placebo based on this measure (page 313, first paragraph; Table 2).

Thus, methodology of Kong et al. provides statistically significant and clinically approved results. As to Applicants' statement that Applicants' methods are based on "commonly-accepted mechanisms of serotonin uptake and regulation", Applicants' have not proven this fact. Further, Applicants' claim that decreased serotonin transporter expression and decreased serotonin uptake are associated with the short (or deletion) allele, therefore, decreased serotonin uptake would render any serotonin receptor antagonist less effective. However, this argument is based on the assumption that the serotonin receptor is the only receptor which takes up serotonin, which is not the case at all. As pointed out by Gershon, there are other receptors which serve as a backup system for serotonin uptake, such as dopamine transporter and organic cation transporters (OCTs) 1 and 3 (page S31, third paragraph). Further, the desensitization due to decreased serotonin uptake affects not only the 5-HT<sub>3</sub> receptor, but also the 5-HT, 5-HT<sub>1P</sub> and 5-HT<sub>4</sub> receptors, and the desensitization of these receptors changes the IBS symptoms (page S31, third paragraph). Therefore, claiming that there is a direct link between the amount of 5-HT<sub>3</sub> receptor and IBS symptoms is an oversimplification. This is also response to Applicants' arguments about the irrelevance of the Gershon reference. Until the relationship between serotonin and all of its receptors and receptor desensitization and IBS symptoms are understood, studies like Applicants' will produce conflicting results. The large

Art Unit: 1637

number of receptors potentially involved in etiology of the IBS symptoms is reflected in the Camilleri review cited above. On pages 1241-1244 Camilleri lists agents affecting the following receptors: 5-HT<sub>3</sub>, 5-HT<sub>4</sub>, 5-HT<sub>1A</sub>, 5-HT<sub>2B</sub>, NK<sub>1</sub>, NK A/B, NK<sub>2</sub>, NK<sub>3</sub>, opioid receptors, CRF, alpha-2 adrenergic receptor, CCK-A and cannabinoid CB-1 receptors.

Regarding the relevance of the Scherl et al. reference, the gender issue is very relevant. Kong et al. Studied 219 females. Applicants' study, which included 11 males and 12 females concluded that the responsiveness to alosetron was greater in females than males (page 14, lines 6-9). Therefore, it is one of the uncertainty factors that may contribute to the overall outcome of the study. With regards to the Pata et al. reference, it is very much relevant to the current study, since it shows that there is no statistical difference in the percentage of population with the three different SERT gene polymorphisms between general population and IBS patients (Table 2). Further, Pata et al. found that the long/long genotype was present at the same percentage in a control group and constipation-predominant, diarrhea-predominant and diarrhea-constipation group (see Table 4), whereas the long/short genotype was found at higher frequency in the diarrhea-predominant group. Therefore, numbers of patients representative of each type of polymorphism might influence the final results of the trial.

In conclusion, taking into account that results of Kong et al. were obtained using clinically approved methodology and provided a statistically significant result which contradicts Applicants', and the fact that prior and current art provides evidence for enormous complexity of the problem of etiology and treatment of IBS, Applicants' method requires undue experimentation.

The rejection is maintained.

***Claim Rejections - 35 USC § 112***

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

Art Unit: 1637

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1, 5 and 8-14 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

“Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in *Ex parte Forman*. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.”

The nature of the invention and breadth of claims

Claims 1, 5 and 8-14 are broadly drawn to methods of for predicting patient's responsiveness to a 5-HT3 receptor antagonist, alosetron, based on determination of the genotype of the promoter region of patient's serotonin transporter (5-HTTP) gene, by correlating the presence of the long/long (= ins/ins) variant with greater responsiveness to the 5-HT3 receptor antagonist. However, as will be further discussed, there is no support in the specification and prior art for the method. The invention is a class of invention which the CAFC has characterized as “the unpredictable arts such as chemistry and biology.” *Mycogen Plant Sci., Inc. v. Monsanto Co.*, 243 F.3d 1316, 1330 (Fed. Cir. 2001).



The amount of direction and guidance presented

Applicants describe serotonin (5-hydroxytryptamine or 5-HT) as a neurotransmitter that modulates sensorimotor functions in the digestive tract (page 1, lines 12-18). Applicants state that clinical trials established a beneficial effect of alosetron, a 5-HT<sub>3</sub> receptor antagonist, in the relief of irritable bowel syndrome (IBS) symptoms (page 1, lines 26-28; page 4, lines 15-22). Applicants assert that effectiveness of the 5-HT<sub>3</sub> antagonist treatment may be related to the genotype in the promoter region of the 5-HTTP gene (page 2, lines 6-16). Applicants provide guidance of how to determine presence of the 5-HTTP gene promoter region polymorphism (page 5, lines 27-32; page 6), how to correlate the genotype with patient's responsiveness to the 5-HT<sub>3</sub> antagonist, using such measures as colonic transit time, for example (page 7, 8; page 9, lines 1-15), and how to effect treatment of patients with diarrhea-predominant IBS (page 9, lines 18-32; page 10, lines 1-26).

The presence or absence of working examples

Applicants conducted a study of 23 patients with diarrhea-predominant IBS, who were enrolled in therapeutic trial with alosetron (Example 1). Patients' genotypes of the 5-HTTP gene promoter region were determined (Example 3). As a measure of alosetron effectiveness, measurement of colonic transit was performed (Example 2). In Example 6, Applicants present a conclusion that long/long variant of the 5-HTTP gene promoter region was associated with a higher response to alosetron, as measured by colonic transit.

The unpredictability of the art and the state of the prior art

Applicants results contradict result of a study by Kong et al. (WO 2001/61039; cited in the previous office action), in which 219 female human subjects enrolled in clinical trial for treatment of IBS with alosetron were genotyped to determine the variant of the promoter in the 5-HTTP gene

Art Unit: 1637

(Example 1). The genotypes were correlated with subjects' response to alosetron (Example 2), as assessed by relief of IBS symptoms, and it was found that subjects with the del/del (= short/short) genotype showed increased therapeutic response to alosetron (Fig. 3), which is directly opposite to Applicants' findings. One reason for this may be a smaller size population sample of Applicants' study, but, as indicated by the publications cited below, the problem of serotonin-based regulation of digestive tract responses is a very complex one.

For example, as pointed out by Scherl et al. (The Pharmacogenomics J., vol. 3, p. 64-66, 2003), serotonin is a neurotransmitter which binds to more than 20 receptor subtypes, including the non-selective 5-HT<sub>3</sub> receptor (which is a cation channel) and a G-protein 5-HT receptor. Serotonin therefore controls different aspects of the gut's sensorimotor function. The 5-HT<sub>3</sub> receptors influence colonic transit, however, actions of alosetron show gender-related effectiveness, however, even with this respect the findings are not uniform (page 65, second paragraph). Finally, Scherl et al. summarize the results of the study of Camilleri et al. (one of the Applicants), pointing out that

“The investigations were unable to correlate variability in SERT-P polymorphisms with gender-specific enhanced alosetron efficacy. Another limitation of the current study was that few of the patients had the short polymorphism, so that this group was under-represented. Future studies evaluating the role of short polymorphisms of SERT-P in gender-specific clinical responses of D-IBS to 5HT<sub>3</sub> antagonists are required. Pharmacogenomic correlation of serotonin- transporter polymorphisms and alesotron response is a powerful research tool that may aid in stratifying individual variation in clinical response of IBS patients.” (page 65, last paragraph) (emphasis added).

Gershon (Rev. Gastroenterol. Dis., vol. 3, suppl. 2, pp. S25S34, 2003) discusses roles played by serotonin in the functioning of enteric nervous system (ENS).

Gershon points to the feedback relationship between the ENS and CNS (central nervous system) as potentially significant in the pathogenesis of IBS, which is a collection of symptoms, and may, because of limited ways that gut can manifest abnormal behaviour, reflect a variety of disorders (page S27, last paragraph; page 28, first paragraph). Further, the interactions of serotonin (5-HT) within the gut are very complex. 5-HT is secreted by enteroendocrine cells (ECs) in response to intraluminal pressure or chemical stimuli, and plays a role in the initiation of peristaltic and secretory reflexes (page S28, third paragraph; Fig. 2). 5-HT then interacts with a number of receptors:

“Enteric neurons have been found to express 5-HT<sub>1A</sub>, 5-HT<sub>1P</sub>, 5-HT<sub>2A</sub>, 5-HT<sub>2B</sub>, 5-HT<sub>3</sub>, and 5-HT<sub>4</sub> receptors; however, of these, only 5-HT<sub>1P</sub>, 5-HT<sub>3</sub>, and 5-HT<sub>4</sub> exert excitatory actions on enteric neurons. Neither 5-HT<sub>3</sub> nor 5-HT<sub>4</sub> antagonists are able, by themselves, to abolish peristaltic and secretory reflexes, although both types of antagonist can alter intestinal motility. These observations suggest that neither peristaltic nor secretory reflexes are initiated by 5-HT<sub>3</sub> or 5-HT<sub>4</sub> receptors. Instead, these 5-HT receptor subtypes probably modulate mucosa-initiated reflexes by affecting neurotransmission within the ENS and, indeed, it is possible to abolish peristaltic reflexes by inhibiting both 5-HT<sub>3</sub> and 5-HT<sub>4</sub> receptors simultaneously.” (page S28, third paragraph).

Further, Gershon points to the fact that even though alosetron does seem to have an effect in the treatment of IBS symptoms in female patients, it may exert the constipating effect by interfering with small proportion of ENS synapses at which transmission is mediated by 5-HT (page S30, first paragraph). Since the 5-HT<sub>3</sub> receptors are responsible for transmission of signals from the bowel to the brain, antagonists of 5-HT<sub>3</sub> receptor, such as alosetron, are used to alleviate nausea associated

with cancer chemotherapy and symptoms of visceral hypersensitivity of diarrhea-predominant sensitivity in IBS (page S30, third paragraph).

The role of 5-HT transporter (or SERT) is to remove serotonin from circulation. If SERT is inhibited, 5-HT receptors become desensitized and peristaltic reflexes are lost, as observed in mice which lack SERT. The action of 5-HT leads in such mice to diarrhea, but as the receptors become desensitized in the constant presence of 5-HT, the colorectal motility slows and mice become constipated. This cycle mimics symptoms of IBS patients (page S31, second paragraph). The reason that the mice lacking SERT or humans having SERT not operating properly survive, is the fact that other transporters, such as dopamine transporter (DAT) and organic cation transporters (OCTs) are able to reuptake 5-HT, but to a much lesser extent (page S31, third paragraph).

Finally, Gershon describes the self-correcting mechanism of 5-HT inactivation: “The relationship among neurotransmitters, receptors, and transporters, which are collectively responsible for neurotransmission, is so closely interknit that a perturbation in one affects others. As a result, the sensitivity of 5-HT<sub>3</sub> receptors and their propensity to become desensitized both change in SERT knockout mice. The concentration-effect curve for activation of 5-HT<sub>3</sub> receptors shifts to the right, indicating that the 5-HT sensitivity of these receptors decreases. The receptors also become desensitized more readily. These changes are secondary to a downregulation in the expression of the B subunit of the 5-HT<sub>3</sub> receptor. (The receptor is a dimer of A and B subunits.) Both the decrease in sensitivity and the increased tendency of the receptors to become desensitized can be characterized as adaptations to an internal milieu of increased 5-HT availability. Both changes tend to prevent the effects of receptor stimulation from becoming excessive.” Therefore, as can be seen from the above facts, interplay between the serotonin receptors and transporters is a very complex one, and the role played by either the serotonin transporter or 5-HT<sub>3</sub> receptor in IBS is not clear.

A study performed by Pata et al. (Am. J. Gastroenter., vol. 97, pp. 1780-1784, 2002) examined a relationship between the SERT gene polymorphisms and the IBS. Pata et al. examined the promoter region polymorphism in 54 patients with IBS and 91 healthy subjects (Abstract; page 1781, paragraphs 1-6). They also divided the IBS patients into three groups, diarrhea-predominant (n = 18), constipation-predominant (n = 26) and alternating diarrhea and constipation (n = 10) (Abstract). Pata et al. Made the following conclusions from examination of the data: a) there is no statistically significant difference in the presence of the SERT gene promoter region polymorphism between IBS and control groups (Table 2); b) the S/S (= short/short) genotype frequency was higher in the constipation-predominant group as compared to the diarrhea-predominant and diarrhea-constipation groups, but not significantly different from the control group (page 1782, first paragraph); c) the S/S (= short/short) genotype frequency was lower in the diarrhea-predominant and diarrhea-constipation groups, and lower than in the control group (page 1782, first paragraph); d) no difference was found between the frequencies of L/L (= long/long) genotype within the IBS groups and between the IBS and control group (page 1782, first paragraph); and, e) the L/S (= long/short) genotype frequency was higher in the diarrhea-predominant group as compared to the constipation-predominant and diarrhea-constipation groups, and higher than in the control group, but there was no significant difference in the L/S genotype frequency between the three IBS groups (page 1782, first paragraph). Pata et al. conclude with the following statements:

“... the presence of the S/S allele may be acting as a protecting factor for diarrhea, so one may speculate that serotonin uptake was slower in constipation predominant patients than in diarrhea predominant and diarrhea constipation patients. This reflection appears to be at odds with the bowel motility-increasing effect that serotonin is known to have, but it should not be forgotten that studies investigating the relationship between IBS and serotonin have been concerned with 5-

HT receptors and postreceptor events (citation omitted). There are not enough studies attempting to determine the relationship between the SERT's gene functional capacity and receptor interaction and bowel functioning.." (emphasis added; page 1782, last paragraph; page 1783, first paragraph).

"In conclusion, it was found that SERT is not a key factor in determining whether or not an individual will get IBS" (page 1783, last paragraph).

Therefore, the overall picture that emerges from the above publications is of uncertain correlation between the genotype of the SERT gene promoter region and IBS, lack of clarity of the roles played by SERT and 5-HT<sub>3</sub> receptors in IBS, as well as very complex 5-HT transporter-receptor interactions and feedback interactions between ENS and CNS, which make it difficult to determine with certainty that any single gene or receptor is responsible for IBS symptoms.

#### Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there is significant number of parameters which would have to be studied to determine whether treatment with 5-HT<sub>3</sub> receptor antagonists in any disease (including IBS) for which such antagonists are used correlates with the promoter region polymorphism of the SERT gene. First, large-scale population study would have to be performed to correlate a presence of the promoter region polymorphism of the SERT gene with any disease in which 5-HT<sub>3</sub> receptor antagonists are used. Then it would need to be determined whether any of these compounds affect any other 5-HT receptors or transporters. Finally, functional interactions between SERT and 5-HT<sub>3</sub> receptors in any type of disease suspected on SERT involvement would need to be determined. This would require years of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

#### Conclusion

In the instant case, as discussed above, in a highly unpredictable art where the antagonist-receptor effects in vivo depend upon numerous known and unknown parameters such as the complex interactions of 5-HT receptors and transporters, the factor of unpredictability weighs heavily in favor of undue experimentation. Further, the prior art and the specification provides insufficient guidance to overcome the art recognized problems in the use of the 5-HT<sub>3</sub> receptor antagonists for in vivo treatment of IBS. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of a working example and the contradictory teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

6. No references were found teaching or suggesting claims 1, 5 and 8-14, but they are rejected for reasons given above.

### ***Conclusion***

7. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be

calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.


Any inquiry concerning this communication or earlier communications from the examiner should be directed to Teresa E Strzelecka whose telephone number is (571) 272-0789. The examiner can normally be reached on M-F (8:30-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

TS

August 9, 2004

  
JEFFREY FREDMAN  
PRIMARY EXAMINER

8/11/04